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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,953	10/03/2000	Hiroshi Kubota	320727.50401.	7343

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/678,953	KUBOTA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 6/17/04 has been entered. Claims 1-24 are pending. Claims 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11 (Filed 12/4/01).

Election/Restrictions

This application contains claims 21-24 which are drawn to an invention nonelected with traverse in Paper No. 11 (12/4/01). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-20 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The prior rejection of claims 1 and 14 as vague and indefinite is maintained. The claims recite that the composition comprises isolated single-cell bipotent hepatic progenitors. It is unclear what the term "single-cell" encompasses and the specification fails to provide a definition for the term. For example, the term could mean a single bipotent hepatic progenitor cell in a composition of other cells. Further, the dependent claims recite properties for the composition of cells and it is unclear what is encompassed by these specific properties (*.e.g,* that they express at least one MHC class Ib antigen, that they express ICAM-1). For example, can the bipotent hepatic progenitor cells have any combination of these properties? These properties are inherent to the bipotent hepatic progenitor cells, and thus, it is unclear how the dependent claims are further limiting. Claims 2-13 and 15-20 depend from claims 1 and 14, respectively.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Sargiacomo *et al.* [**J. of Hepatology**, 28:480-490, 1998], as further evidenced by Haruna [cited in the prior Office action].

The claims are directed to compositions comprising isolated single-cell bipotent hepatic progenitor cells which express at least one ICAM antigen and do not express MHC class 1a antigen, wherein the bipotent hepatic progenitors have the capacity to differentiate when exposed to differentiation-inducing growth conditions.

Applicants argue that Sargiacomo should be withdrawn because they do not disclose each and every element of those amended claims, either inherently or explicity which is required for a *prima facie* showing of anticipation. Particularly, because amended claim 1 is directed to a composition comprising isolated **single-cell** bipotent hepatic progenitors cells which express at least one ICAM antigen and do not express MHC class 1a antigen, wherein the bipotent hepatic progenitors **have the capacity to differentiate when exposed to differentiation-inducing growth conditions**. (*Emphasis in the original*). Thus, Applicants argue that although Sargiacomo teach the isolation and identification of bipotent liver progenitor cells from fetal livers, they do not teach or suggest isolated single-cell hepatic progenitors, nor do they teach the identification of liver progenitors capable of differentiation when exposed to differentiation-inducing growth factors. Further, Applicants argue that the teachings of Haruna do not evidence the claimed invention, nor do they cure the deficiencies of Sargiacomo. Applicants argue that Sargiacomo teach a fetal liver culture system which allows morphogenetic interactions consistent with the development of hepatic function, and that

fundamental to their method is the intact "multi-size spherical hepatic units" which are seeded into culture medium to being the growth process so that the hepatic architecture would be present. Thus, Applicants argue that the importance of the integrity of these heptic units to the Sargiacomo method is indicated by the statement that, "[A]ll the heptic specimens used for preparing the human FLCC were immediately checked for structural integrity by LM." Further, Applicants argue that because Sargiacomo teach intact 3-D cell clusters a cure to deficiencies noted in the art for maintaining isolated hepatocytes in culture, Applicants argue that they do not teach the claimed invention, but actually teach away from single-cell culture methods. See pp. 8-96 of the Response.

This is not found to be persuasive. The claims merely require that the composition comprise isolated single-cell bipotent hepatic progenitors. As such, any composition with hepatic progenitor cells would consist of single cells of hepatic progenitor cells. The breadth of the claims read on, for example, an isolated fetal liver, or minced-up fetal liver, and further embodiments, such as claim 14, which states "their progeny" can read on cells differentiated from the hepatic progenitors, and thus, any liver cells. Thus, the art, as taught by Sargiacomo anticipates the claimed invention because the cell clusters would be made up of "single-cell" bipotent hepatic progenitors, as required by the claims. Furthermore, it is noted that Sargiacomo teaches control cultures, wherein the fetal liver cells were counted as monocellular suspensions, which would also comprise of single cells. See p. 481,

col. 2, 1st full ¶, lines 7-10. It is maintained that Sargiacomo's teaching of cultures of human fetal liver cells, with the evidence provided by Haruna, who identify bipotent progenitor cells in fetal human livers, wherein the time frame of isolation of the fetal livers overlap, would inherently contain bipotent hepatic progenitor cells. Furthermore, Applicants' arguments that Sargiacomo do not teach that the bipotent hepatic progenitors would have the capacity to differentiate when exposed to differentiation-inducing growth factors is not found to be persuasive because such properties are inherent to the cells. See prior Office action, p. 3-4, bridging ¶ and *In re* Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977), *In re* Spada, 911F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Applicants argue that Sargiacomo does not even indicate that bipotent hepatic progenitors exist within the cell cultures taught by Sargiacomo. Applicants argue that inasmuch that Sargiacomo begins cell culture with intact hepatic units (i.e., **not the single-cell bipotent hepatic progenitors of the presently claimed invention**) (*emphasis in the original*), it seems likely that differentiated hepatocytes and biliary cell cultures were present in the initial cell culture. See p. 9, 1st ¶ of the Response. This is not found to be persuasive. The claims require a composition that comprises single-cell bipotent hepatic progenitor cells. Thus, whether or not Sargiacomo's cells contain differentiated hepatocytes or biliary cell cultures in the initial cell culture is not germane to the instant argument because the claims do not require a pure composition of isolated single-cell bipotent hepatic progenitor cells.

Applicants argue that because Sargiacomo do not perform any of the tests taught by Applicants, there would be no way to know whether such progenitors are present. This is not found to be persuasive. Applicants have provided no evidence or teachings of record to show that the cells as taught by Sargiacomo would not contain the progenitor cells; further, it is noted that the arguments of counsel cannot take the place of evidence in the record. See *In re* Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965) and MPEP §716.01. Applicants have not provided an appropriate affidavit or declaration provided sufficient evidence that the cells as taught by Sargiacomo would not contain bipotent hepatic progenitor cells, as instantly claimed. Accordingly, the rejection is maintained.

Applicants argue that because Haruna teach the immunoperoxidase staining of fomalin-fixed paraffin sections of intact liver, and thus, it would not be possibl eto determine if the cells as taught by Haruna would be present in the Sargiacomo cell preparation. Applicants further argue that the application of the Haruna identification methods to the cultures of Sargiacomo would not yield the single cell bipotent hepatic progenitor cells of the instant invention having the capacity to differentiate when exposed to differentiation-inducing growth factors. Further, that one of skill in the art would note that the cells as taught by Haruna would no longer be viable because they have been subjected to formalin fixation. See p. 9-10 of the Response.

Applicants' arguments are not found to be persuasive. It is reiterated that the cells as taught by Sargiacomo are obtained from intact fetal livers, dissociated and then seeded. See p. 481, Experimental Procedures. Thus, the cell preparations would contain all the cells that an intact fetal liver would contain. Thus, Haruna provides evidence of bipotent progenitor cells in a human fetal liver. As Sargiacomo's cells are disclosed to be isolated from human fetal livers, as are those cells claimed by Applicant, as well as those from Haruna, the cells would reasonably be expected to have the same physical and biochemical properties. As stated in the preceding paragraphs, a chemical composition and its properties are inseparable. With regard to the claimed limitation of the cells having the capacity to differentiate when exposed to differentiation-inducing growth factors, it is reiterated that because the cells as taught by Sargiacomo, as evidenced by Haruna, contain bipotent progenitor cells, the capacity of these cells to differentiate would be inherent to the cells. Furthermore, the cells of Sargiacomo are not formalin-fixed, and are viable, thus, there would be no reason to believe that these cells would not be able to differentiate when exposed to differentiation-inducing growth factors as required by the claims.

Accordingly, it is maintained that Sargiacomo anticipate the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

tnt
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